Exhibit A

Curriculum Vitae

PART I: General Information

Name: **Daniel S. Kohane MD, PhD**
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Place of Birth: Geneva, Switzerland

Education

Year	Degree (s)	Institution
1965-1979	International Baccalaureate.	International School of Geneva.
1979-1983	B.A. in Biology	University of Pennsylvania.
1983-1990	Medical doctorate Ph.D. in Physiology	Boston University School of Medicine.

Postdoctoral Training

Year	Title	Specialty	Place of Training
1990-1991	Intern	Pediatrics	Boston Children's Hospital.
1991-1993	Resident	Pediatrics	Boston Children's Hospital.
1993-1995	Resident	Anesthesia	Mass. General Hospital.
1995-1997	Fellow	Pediatric Critical Care	Boston Children's Hospital

Licensure and Certification

1994	Board Certification in Pediatrics
1996	Board Certification in Anesthesia
1998	Board Certification in Pediatric Critical Care
1998	Full Medical License, Massachusetts

Academic Appointments

1997	Instructor in Pediatrics, Harvard Medical School.
2000	Assistant Professor of Pediatrics, Harvard Medical School.

Hospital Appointments

1997	Assistant in Pediatrics, Massachusetts General Hospital.

Other Professional Positions

Year	Title	Institution
1996-	Research Affiliate	Department of Chemical Engineering, Massachusetts Institute of Technology
1997-	Research Associate	Department of Anesthesia, Boston Children's Hospital

Hospital Responsibilities

Year	Role	Institution

1997-	Attending	Pediatric Intensive Care Unit, Mass. General Hospital
1998-	Director	Pediatric Conscious Sedation Service, MGH

Professional Societies

1983-	American Medical Association.
1983-	Massachusetts Medical Society.
1988-	Alpha Omega Alpha Medical Honor Society.
1990-	American Academy of Pediatrics.
1993-	American Society of Anesthesiologists.
1995-	Society of Critical Care Medicine.

Honors

1983	Received B.A. *cum laude*
1989	Elected to Alpha Omega Alpha Medical Honor Society.

Part II: Research, Teaching, and Clinical Contributions

A. Narrative Report of Research, Teaching, and Clinical Contributions

Research

i. Tetrodotoxin for local anesthesia

Initially, my research activities focused on the development of prolonged duration local anesthetics. I performed several studies on the use of highly potent naturally occurring sodium channel blockers for prolonged duration local anesthesia. The first was an in-depth re-examination of the use of tetrodotoxin (TTX) in conjunction with a second drug. We found that it was possible to achieve block durations that dramatically and safely outperform conventional local anesthetics. In a subsequent study, we demonstrated that vanilloid receptor agonists (such as capsaicin) markedly potentiate the efficacy of tetrodotoxin and similar compounds, presumably via inhibition of tetrodotoxin-resistant sodium currents. This interaction was mediated by the vanilloid receptor, as demonstrated by the fact that it could be inhibited by the antagonist, capsazepine. We have studied the effect of functional group substitutions on the activity of saxitoxin (another potent sodium channel blocker). We found that although potency was greatly affected by structural changes, the therapeutic index and the relative proportions of sensory and motor block were only slightly altered. We have performed a more detailed dissection of the effect of adrenergic agonists and antagonists on TTX block. We found that alpha1- and alpha2-adrenergic agonists increased the duration of nerve block from TTX, via a local mechanism (although there was some evidence of a central mechanism with alpha2-adrenergic agonists), due to event that occurred within 75 minutes after injection – even if the subsequent block lasted 16 hours. Another study on examined the effects of high concentrations of adrenergic antagonists on sciatic nerve block by TTX. The hypotheses were that a) high concentrations of beta blockers would affect nerve blockade, as they affect axonal function in isolated cell preparations, b) millimolar concentrations of molecules with one hydrophobic and one alkaline moiety (such as most adrenergic antagonists) would affect analgesia via a GTPase-dependent mechanism. The first hypothesis proved to be correct. The second was partly correct: high concentrations of adrenergic antagonists did markedly prolong TTX block, although it did not appear to be GTPase-mediated (pertussis toxin had no effect).

ii. Pediatric dosing of local anesthetics

A related line of investigation addressed the controversial topic of local anesthetic dosing in pediatrics, as well as the lesser controversy of whether ropivacaine actually produces relatively sensory-selective nerve blockade. We compared ropivacaine to bupivacaine in terms of safety, modality specificity (sensory vs. motor) and effectiveness (duration of block) in a pediatric animal model. We found that while bupivacaine and ropivacaine were equally effective, the latter was much safer as determined by the median effective doses required to achieve various toxic endpoints and the average serum concentration at the time of death. We addressed the important issue of drug dose scaling with size and age, and determined that the current practice of scaling dosage with weight is

probably not optimal. We also confirmed the view that infants are resistant to local anesthetic toxicity compared to older animals.

iii. Controlled released of local anesthetics

Much of my current research focuses on the delivery of local anesthetics in controlled release vehicles. I have been awarded a five-year K-08 grant by the NIH (GM00684), which started on 3/1/2000, and some non-NIH grants to study these and related matters. I have studied novel non-polymeric devices for delivering drugs for local effect while minimizing tissue inflammatory response. We have found that such particles can produce nerve block durations equivalent to those produced by conventional polymeric microspheres, with one-fifth the drug loading. They also appear to have excellent long-term biocompatibility. I have developed a microsphere-based formulation that provides nerve blocks lasting over 9 days in rats (up to 21 days in some cases). This result was published in *Pain* last year and was cited in the International Monitor on Regional Anesthesia and Pain Medicine as one of the key publications in the field.

The above research has resulted in a patent (US Patent 6,326,020).

iv. Intracranial drug delivery and epilepsy

I have also led collaborative projects to provide local sustained drug release in the brain. One project, done with the laboratory of Dr. Michael A. Moskowitz at MGH East, developed a novel intracranial microparticle for drug delivery to the brain (intraparenchymal, intraventricular, and intravascular). Another project, in collaboration with Dr. Gregory Holmes, then at Children's Hospital of Boston, demonstrated the efficacy of locally released encapsulated muscimol in preventing seizures induced by pilocarpine. This research is currently being developed as a story by the Boston Globe.

v. Vaccines

I have developed pH-sensitive microparticles for intracellular delivery of macromolecules. I have shown that these are effective vaccination vehicles *in vitro* and *in vivo* in collaboration with Dr. W. Nicholas Haining at the Dana Farber Cancer Institute. The manuscript is currently being revised following favorable reviews by the *Journal of Immunology*.

vi. Biocompatibility of Biomaterials

We have an interest in implantable devices for a variety of purposes, including BioMEMS and sensing systems. We have studied the biocompatibility of a new tetrahedral amorphous carbon coating and compared it to silicon (the industry standard). We have shown that the method of manufacture of the films is crucial: those with a high preponderance of 3-fold carbon bonding endure much erosion, while those with 4-fold (tetrahedral) bonding do not. This work is being revised for *Biomaterials*.

vii. Prevention of Adhesions

A new focus of my research is now the modulation of adhesive and anti-adhesive forces in preventing adhesion formation in the peritoneum and airway. The former application has been funded by DuPont DeNemours, with a heavy emphasis on drug delivery technology.

Teaching

I currently supervise three undergraduate students and a graduate student. I have previously had a graduate student from Italy who did a one and half year-long rotation with me, and contributed to three manuscripts (as 1st, 2nd, and 4th author), with one other submitted. I was the Reader on a third graduate student's thesis. I have two technicians, two post-docs and a number of undergraduate students. Two fellows from the Pediatric Intensive Care fellowship have joined my research effort as of this year.

I have had numerous collaborations within the Harvard and MIT communities, in which I provide expertise in microencapsulation. As examples, I collaborate with Dr. P.K. Donahoe at the MGH/C, the Mulligan laboratory at Children's, and the Miller lab at the MEEI.

I teach in the clinical and laboratory settings. In the former, I have developed verbal and written clinical teaching tools that are appropriate for the residents, more sophisticated ones for fellows (including multiple choice tests), as well as lectures for a broader audience. In the laboratory, I have supervised numerous undergraduate and masters students, some of whom have received honors or awards for their work. I host a weekly lab meeting for my group in Dr. Langer's lab. As of this year, I have my own course for credit at HST ("Reviewing the biomedical literature"), and will be giving a lecture on drug development in HST 150 (Pharmacology). I have also been an instructor at an MIT course on novel biotechnology hosted by Dr. Langer's laboratory.

Clinical Work

I perform my clinical duties (9 weeks a year) in the pediatric intensive care unit. While my primary role is that of intensivist, I am also the physician in charge of the pediatric conscious sedation service. I have also sat on the pediatric committee on implementing standardized dosing in pediatrics and some other pharmacy-related committees. Last year, I performed a survey of conscious sedation practices at the MassGeneral Hospital for Children, and with others created a framework for a) the implementation of the broader MGH policy regarding conscious sedation to our patient population and, b) facilitating providing such services.

B. Funding (all costs are direct)

Years	Funding Source	PI/Co-PI	Grant Title
2000-2005	NIH GM00684 Start date: 3/1/2000 $125,000 per year	PI (K-08)	Prolonged duration local anesthesia
2001-2002	Sandia Nat'l Labs $50,000 for one year	PI	Biocompatibility of amorphous diamond
2002	CURE $50,000 for one year	co-PI	Encapsulated TTX for epilepsy

2003-2006	DuPont DeNemours co-PI $660,000 over 3 years	Prevention of peritoneal adhesions

C. Report of Current Research Activities

Project	**Role**
Prolonged duration local anesthesia	PI
Prevention of peritoneal adhesions	co-PI
DNA and protein vaccines	co-PI
Controlled release of drugs to the central nervous system	co-PI
Controlled release of anticonvulsant medication to treat focal seizures	co-PI
Controlled release of nucleic acids and proteins	co-PI
pH-triggered drug release	co-PI
Controlled release of angiogenic molecules	co-PI
Biocompatibility of implants	co-PI

D. Report of Teaching

1. Local Contributions

1997 –99 **Weekly Seminar for Fellows (32 times per year): Selected Topics in Pediatric Critical Care.**
Lecturer - Moderator
Preparation: 2 hours per session (every session is new). Contact time: 1 hour.
Attendance: 4-6 fellows

1998+ **Quarterly Multiple Choice exam in Pediatric Critical Care with discussion.**
Create new exam, discussion moderator
Preparation: 6 hours per session. Contact time: 1 hour.
Attendance: 4-6 fellows

1997 + **Daily Teaching Conference to fellows and residents**
Lecturer (when on service). Contact time: 1 hour.
Attendance: 1 fellow, 3 residents, 0-2 medical students

1997-98 **Quarterly Mock Codes on Pediatric Service**
Organizer and presenter
Preparation: 2 hours per session. Contact time: 1 hour.
Attendance: variable number of residents and medical students

1997 - 2000 **Lecture to pediatric ER physicians on acute care issues** (twice per year)
Lecturer
Preparation: 2 hours per session. Contact time: 1 hour.
Attendance: variable number of attendings, residents and medical students

1997 **Pediatric Anesthesia/Surgery Grand Rounds**
Invited Speaker
"Prolonged duration local anesthesia"

1998 **Pediatric Departmental Research Symposium**
Lecturer

"Synergistic local anesthetic effects of site 1 sodium channel blockers and vanilloid receptor agonists when injected at the sciatic nerve *in vivo*".

1998 **Pediatric Research Forum**
Lecturer
"Sciatic nerve blockade in infant, adolescent and adult rats: a comparison of ropivacaine with bupivacaine."

1999 + **PICU fellows' conference.** Approximately 9-12 lectures to fellows per year.

2003 **Lecture to MGH residents**. "Keepin' It Real Wit Respiratory Physiology."

2004 **HST 150**
Lecturer
"Development of a New Formulation."

2004 **HST (Course number TBA)**
Course Director
"Reviewing the biomedical literature." (3 credits)

Special Accomplishments.

1. I have produced a body of case-based discussions that are specifically designed to provide instruction at a level that is suitable for pediatric ICU fellows. These consist of a case analysis using a Socratic method modeled on the Anesthesiology oral examinations. This is followed by a critique of fellow responses and conclusions by the instructor. A series of take-home multiple-choice quizzes are used to encourage reading. There is an emphasis on physiology (which is natural given that I have a Ph.D. in the topic).
2. A number of students (mostly from MIT, but also from Harvard, Cornell, Bowdoin, Boston University and the University of Utrecht, Holland) have been under my supervision in the laboratory. One student (from Harvard) received a *magna cum laude* evaluation for her thesis work with me. Another won second Prize for a poster presentation of his research (MIT). Two students won competitive research grants. Several have been able to become co-authors on manuscripts. As a result of these successes, I was invited to join the Board of Honors Tutors of the Department of Psychology at Harvard University, where I occasional supervise thesis students. I am also a premedical advisor at MIT. I have discussed my graduate students elsewhere.
3. In response to a request from HST, I designed and implemented a course on reviewing the biomedical literature. The course was approved on 2/1/8/04.

2. Regional, National, and International Contributions

1998 "New directions in prolonged duration local anesthesia." Harvard Medical School Comprehensive Review of Pain Management for the Practicing Physician.

1998 "Recent developments in prolonged duration local anesthesia." Anesthesia Grand Rounds, Children's Hospital, Boston

1998-2002 "Scenarios of Impending Death." Pediatric Emergency Medicine Course of the Massachusetts General Hospital
Also: Bask and Mask Ventilation Work Station

1999+ "Spray dried particles for prolonged duration local anesthesia."

Demonstration/instruction at a Course offered by the Dept. of Chemical Engineering, Massachusetts Institute of Technology

1999+ "Airway problems on transport (how to avoid)." Pediatric Transport Conference, Massachusetts General Hospital

1999 "Sciatic nerve blockade with lipid-protein-sugar particles containing bupivacaine." Sixth World Biomaterials Conference, Hawaii. Oral presentation

2000 Drug Delivery II. Sixth World Biomaterials Conference, Hawaii. Session moderator

2000+ "Lipid-protein-sugar particles." Faculty at a Course offered by the Dept. of Chemical Engineering, Massachusetts Institute of Technology

2000 "Conscious sedation workshop." Pediatric Emergency Medicine Course of the Massachusetts General Hospital

2001 Invited Speaker. "Controlled release of drugs and the anesthesiologist." Anesthesia Grand Rounds, Massachusetts General Hospital

2001 Invited speaker. "Prolonged duration local anesthesia". Innovations Conference, New England Pain Association, Boston, MA.

2002 Invited Speaker. Controlled Release of Site 1 Sodium Channel Blockers for Prolonged Duration Local Anesthesia". Particles 2002, Orlando, FL.

2002 "Rapid Sequence Induction" Pediatric Emergency Medicine Course of the Massachusetts General Hospital Also: Mega-Code Work Station

2003 Invited Speaker. "Controlled release Technology for Drug Delivery to the Nervous System" Dept. of Biomedical Engineering, Cornell U., Ithaca, NY.

2003 Invited Speaker. "Prevention of Peritoneal Adhesions", TechCon 2003 (DuPont), Harrisburg, PA.

2003 Plenary Speaker, Pharmaceutical Track. "Microparticulate Focal Drug Delivery To The Peripheral And Central Nervous Systems". 29th Northeast Bioengineering Conference, Newark, NJ.

2003 Invited Speaker. "Focal drug delivery to the peripheral and central nervous systems using controlled release technology". Yale Medical School, New Haven, CT.

2003 "Conscious Sedation vs. Rapid Sequence Induction" Pediatric Emergency Medicine Course of the Massachusetts General Hospital

2003 "pH-triggered release of macromolecules from spray-dried polymethacrylate microparticles." 7th US-Japan Symposium on Drug Delivery Systems, Maui, Hawaii

2004 Invited Speaker. "Rapid sequence induction." North Shore Children's Hospital, Salem, MA.

2004 Invited Speaker. "Rapid sequence induction." Medflight, Bedford, MA.

2004 Invited Speaker. "Biocompatibility." Whitney Symposium (General Electric), Niskayuna ,NY.

2004 Invited Speaker. "Prolonged duration local anesthesia." Genzyme. Cambridge, MA.

2004 Invited Speaker. "Prevention of peritoneal adhesions." Dupont (DMA) Scientific forum, Wilmington, DE.

2004 Invited Speaker. "Pheochromocytoma." Clinicopathological Conference (Case Records of the MGH).

I have not included poster presentations in this list.

E. Report of Clinical Activities

1. My clinical practice is entirely based in the pediatric intensive care unit. Although I am a board-certified anesthesiologist, I do not practice in the operating room at this time. I have directed the pediatric conscious sedation service since 1998.
2. The pediatric ICU is an 8-bed unit. We see many complex cases (liver transplantation, tracheal reconstruction, congenital heart disease repair, acute respiratory distress syndrome, etc.).
3. I have played a role in the revamping of our formulary to reflect my anesthesia background. As director of the conscious sedation service, I set guidelines for patient selection, standardized pharmacotherapy and provide teaching.
4. I have been consulted on several occasions by the Shriner's Burns Center (where I spent six months during my anesthesia training).
5. I was/am on the committees that address pediatric conscious sedation at MGH, the adaptation of a unit-of-use approach to drug delivery on pediatric floors, and other pharmacy-related issues.

PART III: Bibliography

Original Articles

1. **Kohane DS**, Sarzani R, Schwartz JH, Chobanian AV, Brecher P: Stress-induced proteins in aortic smooth muscle cells and aorta of hypertensive rats. Am J Physiol 1990; 258: H1699-705

2. **Kohane DS**, Sankar WN, Shubina M, Hu D, Rifai N, Berde CB: Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of ropivacaine with bupivacaine. Anesthesiology 1998; 89: 1199-208; discussion 10A

3. **Kohane DS**, Yieh J, Lu NT, Langer R, Strichartz GR, Berde CB: A re-examination of tetrodotoxin for prolonged duration local anesthesia. Anesthesiology 1998; 89: 119-31

4. **Kohane DS**, Kuang Y, Lu NT, Langer R, Strichartz GR, Berde CB: Vanilloid receptor agonists potentiate the in vivo local anesthetic activity of percutaneously injected site 1 sodium channel blockers. Anesthesiology 1999; 90: 524-34

5. **Kohane DS**, Lipp M, Kinney RC, Lotan N, Langer R: Sciatic nerve blockade with lipid-protein-sugar particles containing bupivacaine. Pharm Res 2000; 17: 1243-9

6. **Kohane DS**, Lu NT, Gokgol-Kline AC, Shubina M, Kuang Y, Hall S, Strichartz GR, Berde CB: The local anesthetic properties and toxicity of saxitonin homologues for rat sciatic nerve block in vivo. Reg Anesth Pain Med 2000; 25: 52-9

7. **Kohane DS**, Lu NT, Crosa GA, Kuang Y, Berde CB: High concentrations of adrenergic antagonists prolong sciatic nerve blockade by tetrodotoxin. Acta Anaesthesiol Scand 2001; 45: 899-905

8. **Kohane DS**, Lu NT, Cairns BE, Berde CB: Effects of adrenergic agonists and antagonists on tetrodotoxin-induced nerve block. Reg Anesth Pain Med 2001; 26: 239-45

9. Plesnila N, Zinkel S, Le DA, Amin-Hanjani S, Wu Y, Qiu J, Chiarugi A, Thomas SS, **Kohane DS**, Korsmeyer SJ, Moskowitz MA: BID mediates neuronal cell death after oxygen/ glucose deprivation and focal cerebral ischemia. Proc Natl Acad Sci U S A 2001; 98: 15318-23

10. **Kohane DS**, Holmes GL, Chau Y, Zurakowski D, Langer R, Cha BH: Effectiveness of muscimol-containing microparticles against pilocarpine-induced focal seizures. Epilepsia 2002; 43: 1462-8

11. **Kohane DS**, Plesnila N, Thomas SS, Le D, Langer R, Moskowitz MA: Lipid-sugar particles for intracranial drug delivery: safety and biocompatibility. Brain Res 2002; 946: 206-13

12. **Kohane DS**, Lipp M, Kinney RC, Anthony DC, Louis DN, Lotan N, Langer R: Biocompatibility of lipid-protein-sugar particles containing bupivacaine in the epineurium. J Biomed Mater Res 2002; 59: 450-9

13. Fauza DO, **Kohane DS**, Beewukes E, Clayton N, Maher TS: Local anesthetics inhibit myometrial activity in vitro: possible application on preterm labor prevention and treatment. Fetal Diagn Ther 2003; 18: 292-296

14. **Kohane DS**, Smith SE, Louis DN, Colombo G, Ghoroghchian P, Hunfeld NGM, Berde CB, Langer RS: Prolonged duration local anesthesia from tetrodotoxin-enhanced local anesthetic microspheres. Pain 2003; 104: 415-421

15. **Kohane DS**, Anderson DG, Yu C, Langer R: pH-triggered release of macromolecules from spray-dried polymethacrylate microparticles. Pharm Res 2003; 20: 1533-1542

16. Colombo G, Langer R, **Kohane DS**: Effect of excipient composition on the biocompatibility of bupivacaine-containing microparticles at the sciatic nerve. J. Biomed. Mater. Res. 2004; 68A: 651-659
17. Thomas TT, **Kohane DS**, Wang A, Langer R: Microparticulate formulations for controlled release of IL-2. J Pharm Sci 2004; 93: 1100-1109
18. Jia X, Colombo G, Padera R, Langer R, **Kohane DS**: Prolongation of sciatic nerve blockade by in situ crosslinked hyaluronic acid. Biomaterials 2004; 25: 4797-4804
19. LaVan DA, Padera RF, Friedmann TA, Sullivan JP, Langer R, **Kohane DS**: *In Vivo* evaluation of tetrahedral amorphous carbon. Biomaterials 2004; (in press).
20. Barnet C, Tse J, **Kohane DS**: Site 1 sodium channel blockers prolong the duration of sciatic nerve blockade from tricyclic antidepressants. Pain 2004; (in press)
21. Chen PC, Park YJ, Chang LC, **Kohane DS**, Barlett RH, Langer R, Yang VC: Injectable microparticle-gel system for prolonged and localized lidocaine release. I. In vitro characterization. J Biomed Mater Res 2004; (in press)
22. Chen PC, **Kohane DS**, Park YJ, Barlett RH, Langer R, Yang VC: Injectable microparticle-gel system for prolonged and localized lidocaine release. II. In vivo anesthetic effects. J Biomed Mater Res 2004; (in press)
23. Haining HN, Anderson DG, Little SR, von Berwelt-Baildon MS, Cardoso AA, Alves P, Kosmatopoulos K, Nadler LM, Langer R, **Kohane DS**: pH-triggered microparticles for peptide vaccination. J. Immunology 2004; (in press)

Reviews, Chapters, and Editorials

1. **Kohane DS**, Tobin T, Kohane I: Endocrine, mineral and metabolic disease in pediatric intensive care, Textbook of pediatric intensive care. Edited by Rogers MC, Nichols DG. Baltimore, Williams & Wilkins, 1996, pp 1247-1314
2. **Kohane DS**, Tobin T, Kohane I: Endocrine, mineral and metabolic disease, Handbook of pediatric intensive care. Edited by Rogers MC, Helfaer MA. Baltimore, Williams & Wilkins, 1998, pp. 684-730
3. Fricchione G, **Kohane DS**, Daly R, Todres ID: Psychopharmacology in the intensive care unit. New Horizons 1998; 6: 353-362
4. **Kohane DS**, Cheng L-A, Noviski N: Disorders of temperature regulation, Gellis & Kagan's Current Pediatric Therapy, 17th Edition. Edited by Burg. Philadelphia, Harcourt, 2002.
5. **Kohane DS**, Langer R. Biotechnology for Drug Delivery to Improve Patient Compliance. Behavioral Health Management 2004; (in press)
6. **Kohane DS**, Ingerlfinger J. Nine-year old female with headaches, enuresis, recent visual changes, and vomiting. N Engl J Med 2004; (in press)

Patents

1. US Patent 6,326,020. Kohane DS, Berde CB, Strichartz G, Langer RS. Local anesthetic formulations.

Thesis

1. **Kohane DS**. Effects of hypertension on gene expression and fatty acid metabolism in the arterial vasculature [Doctoral dissertation]. Boston. MA: Boston University School of Medicine, 1990. 320 pp.

Other

1. **Kohane DS**, Ringer, S. The Way of the NICU, 1999. This is a pocket manual of neonatology commissioned and published by the Joint Program of Neonatology at Harvard, that has been issued (in various editions) to all residents coming through that program for the past several years.